PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 38147-0045WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US05/03858	International filing date *(day/month/year)* 07 February 2005 (07.02.2005)	Priority date *(day/month/year)* 05 February 2004 (05.02.2004)
International Patent Classification (IPC) or national classification and IPC IPC: Please See Continuation Sheet USPC: 536/23.1,24.3,24.33,24.5;435/6,91.1,325,375;514/44		
Applicant INTRADIGM CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 25 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☒ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 September 2005 (06.09.2005)	05 October 2006 (05.10.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Terra C. Gibbs Telephone No. 571-272-1600

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/03858

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-42 as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the claims:
pages 43-46 as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☒ the drawings:
pages NONE as originally filed/furnished
pages* 13-37 received by this Authority on 06 September 2005
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/03858

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive Step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. Citations and Explanations (Rule 70.7)
Please See Continuation Sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/03858

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The description is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof: Claim 38 is missing from the claim list.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Please See Continuation Sheet

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:

Continuation of IPC:
C07H 21/02(2006.01),**21/04**(2006.01);**C12Q 1/68**(2006.01);**C12P 19/34**(2006.01);**A01N 43/04**(2006.01)

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 11, 13, 8-10, 12, 14, 16, 17, 19, 22, 24, 26, 28, 30, 32, 34, 36, 37, 40, 42, and 44
The opinion as to Novelty was negative (No) with respect to claims 1-7, 15, 18, 20, 21, 23, 25, 27, 29, 31, 33, 35, 39, 41, and 43
The opinion as to Inventive Step was positive (Yes)with respect to claims 17, 19, 22, 24, 26, 28, 30, 32, 34, 36, 37, 40, 42, and 44
The opinion as to Inventive Step was negative(NO) with respect to claims 15, 18, 20, 21, 23, 25, 27, 29, 31, 33, 35, 39, 41, and 43
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-37 and 39-44
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

V. 2. Citations and Explanations:
Claims 1-37 and 39-44 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Claim 13 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a composition comprising a siRNA duplex wherein each duplex inhibits the expression of a gene associated with a disease process, and wherein the composition comprises specific sequences as recited in claim 13.

Claims 8-10, 12, 14, 16, 17, 19, 22, 24, 26, 28, 30, 32, 34, 36, 37, 40, 42, and 44 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method of treating a disease in a subject comprising administering to said subject a composition comprising a siRNA duplex wherein each duplex inhibits the expression of a gene associated with a disease process.

Claims 1-7, 15, 18, 20, 21, 23, 25, 27, 29, 31, 33, 35, 39, 41, and 43 lack an inventive step under PCT Article 33(3) as being obvious over either Shirai et al., Ishibashi et al., GenBank Accession No. AF063658, or GenBank Accession No. NM_001963 in view of Hammond et al. and ElBashir et al.

Supplemental Box

Shirai et al., Ishibashi et al., GenBank Accession No. AF063658, or GenBank Accession No. NM_001963 teach the cDNA and mRNA sequences of different genes associated with a disease process (e.g. TNF alpha, endothelial growth factor receptor (KDR), epidermal growth factor (EGR), etc).

Shirai et al., Ishibashi et al., GenBank Accession No. AF063658, or GenBank Accession No. NM_001963 do not teach nucleic acid inhibitors of genes associated with a disease process.

Hammond et al. teach two methods for silencing specific genes, antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from questionable specificity and incomplete efficacy (see page 110, column 1). Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression.

Elbashir et al. teach dsRNA duplexes 21-23 nucleotides in length with 2 nt 3' overhangs. Elbashir et al. teach 2'-deoxy and 2'-O-methyl modifications to one or both strands. Elbashir et al. teach that modifications are tolerated depending on the location in the duplex. Elbashir et al. teach that substitution of the 2 nt 3' overhangs by 2'-deoxynucleotides had no effect and even the replacement by two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Elbashir et al. teach 2'-deoxythymidines. Elbashir et al. teach an embodiment wherein the siRNA is blunt ended with 21 nucleotides base paired between duplex strands (see figure 1F). Elbashir et al. teach complete substitution of one or both strands of the siRNA duplex, wherein the completely substituted duplex is considered to comprise no ribonucleotides. Elbashir et al. teach that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a nucleic acid inhibitor targeted to a gene associated with a disease process using the sequences taught by either Shirai et al., Ishibashi et al., GenBank Accession No. AF063658, or GenBank Accession No. NM_001963 and the motivation of Hammond et al. and ElBashir et al.

One of ordinary skill in the art would have been motivated to make a siRNA molecule targeted to a gene associated with a disease process for the purpose of inhibiting disease progression via gene silencing and because Hammond et al. teach using siRNA to inhibit gene expression is more sequence specific than using traditional antisense methods and that RNAi is a more potent method, requiring only a few molecules of dsRNA per cell.

One of ordinary skill in the art would have a reasonable expectation of success of making a siRNA molecule targeted to a gene associated with a disease process since one of ordinary skill in the art would reasonably expect for RNAi to serve as an appropriate means to inhibit a gene associated with a disease process because Hammond et al. teach that dsRNAs have been shown to inhibit gene expression in a sequence-specific manner and that RNAi is a potent gene silencing method.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

VIII. The following observations on the clarity of the claims, description, and drawings or on the questions, are made:

Claims 8-10, 12, 14, 16, 17, 19, 22, 24, 26, 28, 30, 32, 34, 36, 37, 40, 42, and 44 objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because the following factors have been considered in formulating this rejection: the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of

Supplemental Box

the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

The instant claims are drawn to methods of treating a disease in a subject, comprising administering a siRNA duplex, wherein the siRNA duplex inhibits expressionof a gene associated with a disease process.

At the time the instant invention was made, the therapeutic use of siRNA molecules was highly unpredictable due to obstacles that continue to hinder the therapeutic application of oligonucleotide-based therapeutics *in vivo* (see for example Hannon et al., Nature, 2004 Vol. 431:371-378; Downward, J., BMJ, 2004 Vol. 328:1245-1428; and Paroo et al., Trends in Biotechnology, 2004 Vol. 22:390-394). Such obstacles include, for example, siRNA duplex stability, delivery, issues of absorption, distribution, metabolism, and excretion. Hannon et al. state, "It is feasible to infuse backbone-modified oligonucleotides *in vivo,* but achieving intracellular delivery at therapeutically effective concentrations is a major challenge. Targeted delivery to specific cell or tissues types is till not a practical reality for oligonucleotide-based therapeutics" (see page 377, second column, first full paragraph). Hannon et al. also state, "Despite considerable hurdles to overcome, it seems likely that RNAi will find a place alongside more conventional approaches in the treatment of diseases, although it is unclear how long we will have to wait to witness the first RNAi-based drug" (see page 377, second column, last paragraph).

Downward, J. outlines that RNA interference can be used as an effective therapeutic strategy, however considerable problems relating to delivery to target cells will have to be solved (see Abstract). Downward further addresses the unpredictability and the problems faced in the siRNA art with the following statements: "Although a big improvement on previous methods, RNA interference has its limitations. Not every sequence works - most researchers get a success rate of about one in three. In addition, although the effects are generally thought to be highly sequence specific, some question marks remain as to whether or not some of the effects seen are "off target"" (see page 1246, last paragraph). Downward adds, "RNA interference clearly has much promise in the laboratory"... "However a huge gap exists between achieving results *in vitro* and in a whole animal or patient" (see page 1247, second column, first paragraph). Downward concludes with, "The major challenge in turning RNA interference into an effective therapeutic strategy is the delivery of the RNA interference agents... to the target cells within the body" (see page 1247, second column).

Paroo et al. address the unpredictability associated with siRNA therapy with the following statements: "In contrast to the great success of synthetic siRNA in mammalian cell culture, there have been few reports employing synthetic siRNA in animals. Developing siRNA for efficient gene silencing *in vivo* is likely to be more challenging and many issues must be addressed before use in animals can become routine". Paroo et al. also state, "Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

The field of siRNA therapy, at the time the instant invention was made and to date, does not provide guidelines by which siRNA molecules can be routinely delivered a subject *in vivo* (whole organism) at a concentration effective to result in methods of treatment as claimed.

In order to practice the invention claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of how to specifically deliver a siRNA molecule to a subject *in vivo* (whole organism) at a concentration effective to result in treating a disease. Additionally, this undue experimentation would include the determination of how to maintain the siRNA duplex, for example *in vivo*, where the art has shown that this is a great challenge. Given the art-recognized unpredictability of the therapeutic application of siRNA *in vivo*, this determination would not be routine and would require undue trial and error experimentation.

Therefore, due to the broad scope of the methods claimed, the state of the art of oligonucleotide-based therapy, the level of unpredictability of *in vivo* (whole organism) methods of using siRNA, the lack of specific guidance for the *in vivo* application of siRNA molecule(s), and the lack of working examples or examples which correlate with the claimed methods, one skilled in the art would not be able to practice the methods claimed, without undue trial and error experimentation.

Appendix II. siRNA Targeted Sequences for Combinational Use

SS1.VEGF pathway

SS1.1. VEGF-A

VEGF gene: human VEGF, Accession : XM_052681, Gene ID: 14781453, mouse VEGF, Accession: M95200, Gene ID: 202350.
20 siRNA candidates were selected:

#	Position	Sequence
VEGF-A-1	64-84	AAGTGGTCCCAGGCTGCACCC
VEGF-A-2	467-487	AAGATCCGCAGACGTGTAAAT
VEGF-A-3	498-518	AAACACAGACTCGCGTTGCAA
VEGF-A-4	499-519	AACACAGACTCGCGTTGCAAG
VEGF-A-5	517-537	AAGGCGAGGCAGCTTGAGTTA
VEGF-A-6	537-557	AAACGAACGTACTTGCAGATG
VEGF-A-7	538-558	AACGAACGTACTTGCAGATGT
VEGF-A-8	542-564	AACGTACTTGCAGATGTGACA
VEGF-A-9	162-182	AATCGAGACCCTGGTGGACAT
VEGF-A-10	338-358	AAGGCCAGCACATAGGAGAGA
VEGF-A-11	92-112	AAGGAGGAGGGCAGAATCATC
VEGF-A-12	386-406	AATGCAGACCAAAGAAAGATA
VEGF-A-13	380-400	AATGTGAATGCAGACCAAAGA
VEGF-A-14	301-321	AACATCACCATGCAGATTATG
VEGF-A-15	451-471	AAGCATTTGTTTGTACAAGAT
VEGF-A-16	116-136	AAGTGGTGAAGTTCATGGATG
VEGF-A-17	401-421	AAGATAGAGCAAGACAAGAAA
VEGF-A-18	421-441	AATCCCTGTGGGCCTTGCTCA
VEGF-A-19	379-499	AAATGTGAATGCAGACCAAAG
VEGF-A-20	262-282	AATGACGAGGGCCTGGAGTGT

SS1.2. VEGF-B

VEGF-B gene: human VEGF-B, Accession : NM_003377.3, Gene ID: 39725673
10 siRNA candidates were selected:

#	Position	Sequence
VEGF-B-1	140-160	AAAGTGGTGTCATGGATAGAT
VEGF-B-2	141-163	AAGTGGTGTCATGGATAGATG
VEGF-B-3	236-258	AAACAGCTGGTGCCCAGCTGC
VEGF-B-4	327-349	AAGTCCGGATGCAGATCCTCA
VEGF-B-5	390-412	AAGAACACAGCCAGTGTGAAT
VEGF-B-6	393-415	AACACAGCCAGTGTGAATGCA
VEGF-B-7	424-446	AAAGGACAGTGCTGTGAAGCC
VEGF-B-8	425-447	AAGGACAGTGCTGTGAAGCCA
VEGF-B-9	440-462	AAGCCAGACAGGGCTGCCACT
VEGF-B-10	670-692	AACCCAGACACCTGCAGGTGC

FIG. 17

AMENDED SHEET

SS1.3.

VEGF R-1 gene: human VEGF-R1, (hFLT-1), Accession : AF063657, Gene ID: 3132830,
mouse VEGF-R1, (mFLT-1), Accession: D88689, Gene ID: 2809068), 20 siRNA candidates were selected:

#	Position	Sequence
VEGFR1-1	1706-1728	AAGGAGAGGACCTGAAACTGT
VEGFR1-2	2698-2720	AAGCAAGGAGGGCCTCTGATG
VEGFR1-3	2702-2724	AAGGAGGGCCTCTGATGGTGA
VEGFR1-4	2755-2777	AACTACCTCAAGAGCAAACGT
VEGFR1-5	3014-3036	AAGTGGCCAGAGGCATGGAGT
VEGFR1-6	3048-3070	AAAGTGCATTCATCGGGACCT
VEGFR1-7	3049-3071	AAGTGCATTCATCGGGACCTG
VEGFR1-8	2140-2160	AGCACGCTGTTTATTGAAAGA
VEGFR1-9	568-588	AAGGGCTTCATCATATCAAAT
VEGFR1-10	215-235	AAAGGCTGAGCATAACTAAAT
VEGFR1-11	2352-2372	AAGGTCTTCTTCTGAAATAAA
VEGFR1-12	3517-3537	AATGCCATACTGACAGGAAAT
VEGFR1-13	1190-1210	AAGAGGATGCAGGGAATTATA
VEGFR1-14	834-854	AAGGCGACGAATTGACCAAAG
VEGFR1-15	89-109	AAGATCCTGAACTGAGTTTAA
VEGFR1-16	216-236	AAGGCTGAGCATAACTAAATC
VEGFR1-17	3429-3449	AAGGCCAAGATTTGCAGAACT
VEGFR1-18	967-987	AACACCTCAGTGCATATATAT
VEGFR1-19	567-587	AAAGGGCTTCATCATATCAAA
VEGFR1-20	1938-1958	AATCCTCCAGAAGAAAGAAAT

SS1.4.

VEGF R-2 gene: human VEGF-R2, (hKDR), Accession : AF063658, Gene ID: 3132832, mouse VEGF-R2, (mFLK-1), Accession: X70842, Gene ID: 57923), 20 siRNA candidates were selected:

#	Position	Sequence
VEGFR2-1	523-545	AACAGAATTTCCTGGGACAGC
VEGFR2-2	2387-2409	AACTGAAGACAGGCTACTTGT
VEGFR2-3	2989-3011	AAGGACTTCCTGACCTTGGAG
VEGFR2-4	3032-3054	AAGTGGCTAAGGGCATGGAGT
VEGFR2-5	3040-3062	AAGGGCATGGAGTTCTTGGCA
VEGFR2-6	3401-3423	AAATGTACCAGACCATGCTGG
VEGFR2-7	3632-3654	AATTCCATTATGACAACACAG
VEGFR2-8	3676-3698	AACAGTAAGCGAAAGAGCCGG
VEGFR2-9	3641-3661	ATGACAACACAGCAGGAATCA
VEGFR2-10	357-377	AAGCTCAGCACACAGAAAGAC
VEGFR2-11	493-513	AATGCGGCGGTGGTGACAGTA
VEGFR2-12	1837-1857	AATGCCACCATGTTCTCTAAT
VEGFR2-13	2969-2989	AAGCTCCTGAAGATCTGTATA
VEGFR2-14	2549-2569	AAGCAGATGCCTTTGGAATTG
VEGFR2-15	3906-3926	AAGCGGCTACCAGTCCGGATA

FIG. 17 (Cont'd.)

VEGFR2-16	2941-2961	AAGTCCCTCAGTGATGTAGAA
VEGFR2-17	304-324	AAGTGCTTCTACCGGGAAACT
VEGFR2-18	2862-2882	AATCCCTGTGGATCTGAAACG
VEGFR2-19	130-150	AAGGCTAATACAACTCTTCAA
VEGFR2-20	1204-1224	AATCCCATTTCAAAGGAGAAG

FIG. 17 (Cont'd.)

SS2.EGF Pathway

SS2.1.

EGF gene: Human EGF, Accession: NM_001963, Gene ID: 6031163.
20 siRNA candidates were selected:

#	Position	Sequence
EGF-1	2042-2062	AAGTGGATAGAGAGAGCTAAT
EGF-2	3873-3893	AAGGCTGCTGGATTCCAGTAT
EGF-3	2426-2446	AAGCAGTCTGTGATTGAAATG
EGF-4	2621-2641	AAGCCCTCATCACTGGTTGTG
EGF-5	1273-1293	AAAGGACATGGTTAGAATTAA
EGF-6	2328-2348	AAGGCCTTGGCCGTCTGGTTA
EGF-7	174-194	AAGGGTGTCAGGTATTTCTTA
EGF-8	3922-3942	AATGGAGCGAAGCTTTCATAT
EGF-9	1496-1516	AAGTACTGTGAAGATGTTAAT
EGF-10	1274-1294	AAGGACATGGTTAGAATTAAC
EGF-11	531-551	AAGGTACTCTCGCAGGAAATG
EGF-12	2686-2706	AAACGGAGGCTGTGAACATAT
EGF-13	2263-2283	AATGGCCAAGAGATTATTCTG
EGF-14	1292-1312	AACCTCCATTCATCATTTGTA
EGF-15	261-281	AAGGTCTCTCAGTTGAAGAAA
EGF-16	3218-3238	AATGCCAGCTGCACAAATACA
EGF-17	1019-1039	AAGGCTCTGTTGGAGACATCA
EGF-18	2576-2596	AAGAGGACTGGCAAAGATAGA
EGF-19	760-780	AAGGCAAGAGAGAGTATGTAA
EGF-20	765-785	AAGAGAGAGTATGTAATATAG

FIG. 17 (Cont'd.)

SS2.2.
EGF R gene: Human EGF-R, Accession: NM_005228, Gene ID: 41327737), mouse EGF-R, Accession : NM_207655, Gene ID: 46560581, 5 siRNA candidates were selected:

#	Position	Sequence
EGFR-1	483-505	AAAGACCATCCAGGAGGTGGC
EGFR-2	2869-2889	AAAGTGCCTATCAAGTGGATG
EGFR-3	2870-2890	AAGTGCCTATCAAGTGGATGG
EGFR-4	3751-3771	AACCCTGACTACCAGCAGGAC
EGFR-5	3755-3775	CTGACTACCAGCAGGACTTCT

SS2.3.
HER-2 gene: Human HER-2, Accession: M11730, Gene ID:183986, mouse HER-2, Accession : BC053078, Gene ID: 31419374, 5 siRNA candidates were selected:

#	Position	Sequence
HER2-1	1255-1275	AAGATCTTTGGGAGCCTGGCA
HER2-2	1253-1273	AAGAAGATCTTTGGGAGCCTG
HER2-3	2797-2817	AAGGTGCCCATCAAGTGGATG
HER2-4	3019-3039	AAATGTTGGATGATTGACTCT
HER2-5	3805-3825	AACCTCTATTACTGGGACCAG

SS2.4.
HER-3 gene: Human HER-3, Accession: M34309, Gene ID:183990, mouse HER-3, Accession : XM_125954, Gene ID: 38091004, 13 siRNA candidates were selected:

#	Position	Sequence
HER3-1	678-698	AATTGACTGGAGGGACATCGT
HER3-2	1264-1284	AAGATCCTGGGCAACCTGGAC
HER3-3	1537-1557	AAGGAAATTAGTGCTGGGCGT
HER3-4	2404-2424	AAGATTCCAGTCTGCATTAAA
HER3-5	2857-2877	AAATACACACACCAGAGTGAT
HER3-6	2858-2878	AATACACACACCAGAGTGATG
HER3-7	3770-3790	AAGATGAAGATGAGGAGTATG
HER3-8	3776-3796	AACCTCTATTACTGGGACCAG
HER3-9	1118-1138	CTGACAAGATGGAAGTAGATA
HER3-10	1119-1139	TGACAAGATGGAAGTAGATAA
HER3-11	2402-2422	TCAAGATTCCAGTCTGCATTA
HER3-12	2403-2423	CAAGATTCCAGTCTGCATTAA
HER3-13	2805-2825	TGAGGCCAAGACTCCAATTAA

FIG. 17 (Cont'd.)

SS2.5.

HER-4 gene: Human HER-4, Accession: NM_005235, Gene ID:4885214, mouse HER-4, Accession : XM_136682, Gene ID: 38049556. 7 siRNA candidates were selected:

#	Position	Sequence
HER4-1	462-482	AAATGGTGGAGTCTATGTAGA
HER4-2	463-483	AATGGTGGAGTCTATGTAGAC
HER4-3	731-751	AATGTGCTGGAGGCTGCTCAG
HER4-4	838-860	AATCCAACCACCTTTCAACTG
HER4-5	1227-1247	AACAGGTTTCCTGAACATACA
HER4-6	1450-1470	AACTGGACAACACTCTTCAGC
HER4-7	1909-1929	AACGGTCCCACTAGTCATGAC

FIG. 17 (Cont'd.)

SS3. FGF Pathway

SS3.1.
FGF-2 gene: Human FGF-2 (basic FGF), Accession: NM_002006, Gene ID: 41352694.
20 siRNA candidates were selected:

#	Position	Sequence
FGF-2-1	630-650	AAGAGCGACCCTCACATCAAG
FGF-2-2	661-681	AAGCAGAAGAGAGAGGAGTTG
FGF-2-3	849-869	AAACGAACTGGGCAGTATAAA
FGF-2-4	880-900	AAACAGGACCTGGGCAGAAAG
FGF-2-5	854-874	AACTGGGCAGTATAAACTTGG
FGF-2-6	648-668	AAGCTACAACTTCAAGCAGAA
FGF-2-7	850-870	AACGAACTGGGCAGTATAAAC
FGF-2-8	881-901	AACAGGACCTGGGCAGAAAGC
FGF-2-9	667-687	AAGAGAGAGGAGTTGTGTCTA
FGF-2-10	723-743	AAGGAAGATGGAAGATTACTG
FGF-2-11	734-754	AAGATTACTGGCTTCTAAATG
FGF-2-12	781-801	AACGATTGGAATCTAATAACT
FGF-2-13	690-710	AAAGGAGTGTGTGCTAACCGT
FGF-2-14	818-838	AAGGAAATACACCAGTTGGTA
FGF-2-15	804-824	AATACTTACCGGTCAAGGAAA
FGF-2-16	750-770	AAATGTGTTACGGATGAGTGT
FGF-2-17	822-842	AAATACACCAGTTGGTATGTG
FGF-2-18	655-675	AACTTCAAGCAGAAGAGAGAG
FGF-2-19	823-843	AATACACCAGTTGGTATGTGG
FGF-2-20	798-818	AACTACAATACTTACCGGTCA

FIG. 17 (Cont'd.)

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SS3.2.

FGF-1 gene: Human FGF-1 (acidic FGF),
transcript variant 1, Accession: NM_000800, Gene ID: 15055546;
transcript variant 2, Accession: NM_033136, Gene ID: 15055540;
transcript variant 3, Accession: NM_033137, Gene ID: 15055544.
20 siRNA candidates were selected:

#	Position	Sequence
FGF-1-1	447-467	AAGGCTGGAGGAGAACCATTA
FGF-1-2	214-234	AAGCCCAAACTCCTCTACTGT
FGF-1-3	190-210	AATCTGCCTCCAGGGAATTAC
FGF-1-4	114-134	AAGCGCCACAAGCAGCAGCTG
FGF-1-5	484-504	AAGAAGCATGCAGAGAAGAAT
FGF-1-6	539-559	AACGCGGTCCTCGGACTCACT
FGF-1-7	460-480	AACCATTACAACACCTATATA
FGF-1-8	97-117	AAGCTCTTTAGTCTTGAAAGC
FGF-1-9	469-489	AACACCTATATATCCAAGAAG
FGF-1-10	221-241	AACTCCTCTACTGTAGCAACG
FGF-1-11	288-308	AAGGGACAGGAGCGACCAGCA
FGF-1-12	487-507	AAGCATGCAGAGAAGAATTGG
FGF-1-13	113-133	AAAGCGCCACAAGCAGCAGCT
FGF-1-14	502-522	AATTGGTTTGTTGGCCTCAAG
FGF-1-15	520-540	AAGAAGAATGGGAGCTGCAAA
FGF-1-16	211-231	AAGAAGCCCAAACTCCTCTAC
FGF-1-17	538-558	AAACGCGGTCCTCGGACTCAC
FGF-1-18	526-546	AATGGGAGCTGCAAACGCGGT
FGF-1-19	220-240	AAACTCCTCTACTGTAGCAAC
FGF-1-20	424-444	AATGAGGAATGTTTGTTCCTG

FIG. 17 (Cont'd.)

SS3.3.

FGFR2 gene: Human FGFR2
transcript variant 1, Accession: NM_000141, Gene ID: 13186239;
transcript variant 2, Accession: NM_022969, Gene ID: 13186252;
transcript variant 3, Accession: NM_022970, Gene ID: 13186254.
transcript variant 4, Accession: NM_022971, Gene ID: 13186256;
transcript variant 5, Accession: NM_022972, Gene ID: 13186258;
transcript variant 6, Accession: NM_022973, Gene ID: 13186260.
transcript variant 7, Accession: NM_022974, Gene ID: 13186262;
transcript variant 8, Accession: NM_022975, Gene ID: 27754768;
transcript variant 9, Accession: NM_022976, Gene ID: 13186266.
transcript variant 10, Accession: NM_023028, Gene ID: 13186268;
transcript variant 11, Accession: NM_023029, Gene ID: 13186242;
transcript variant 12, Accession: NM_023030, Gene ID: 13186270.
transcript variant 13, Accession: NM_023031, Gene ID: 13186272;
20 siRNA candidates were selected:

#	Position	Sequence
FGFR2-1	1368-1388	AAGCCGGACTGCCGGCAAATG
FGFR2-2	2610-2630	AAGCCCTGTTTGATAGAGTAT
FGFR2-3	2088-2108	AAGCAGTGGGAATTGACAAAG
FGFR2-4	2297-2317	AAAGGCAACCTCCGAGAATAC
FGFR2-5	1753-1773	AATCGCCTGTATGGTGGTAAC
FGFR2-6	2010-2030	AATGGGAGTTTCCAAGAGATA
FGFR2-7	699-719	AAGAGCCACCAACCAAATACC
FGFR2-8	2843-2863	AAGCAGTTGGTAGAAGACTTG
FGFR2-9	1187-1207	AAGCAGGAGCATCGCATTGGA
FGFR2-10	1082-1102	AAGCGGCTCCATGCTGTGCCT
FGFR2-11	1557-1577	AAGAGATTGAGGTTCTCTATA
FGFR2-12	1771-1791	AACAGTCATCCTGTGCCGAAT
FGFR2-13	2762-2782	AAGCCAGCCAACTGCACCAAC
FGFR2-14	1178-1198	AAGGAGTTTAAGCAGGAGCAT
FGFR2-15	2151-2171	AAGATGATGCCACAGAGAAAG
FGFR2-16	2745-2765	AAGGACACAGAATGGATAAGC
FGFR2-17	1171-1191	AAACGGGAAGGAGTTTAAGCA
FGFR2-18	1222-1242	AAACCAGCACTGGAGCCTCAT
FGFR2-19	2732-2752	AAGCTGCTGAAGGAAGGACAC
FGFR2-20	1556-1576	AAAGAGATTGAGGTTCTCTAT

FIG. 17 (Cont'd.)

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SS3.4.

FGFR1 gene: Human FGFR1
transcript variant 1, Accession: NM_000604, Gene ID: 13186232;
transcript variant 2, Accession: NM_015850, Gene ID: 13186250;
transcript variant 3, Accession: NM_023105, Gene ID: 13186233.
transcript variant 4, Accession: NM_023106, Gene ID: 13186235;
transcript variant 5, Accession: NM_023107, Gene ID: 13186237;
transcript variant 6, Accession: NM_023108, Gene ID: 13186240.
transcript variant 7, Accession: NM_023109, Gene ID: 13186244;
transcript variant 8, Accession: NM_023110, Gene ID: 13186246;
transcript variant 9, Accession: NM_023111, Gene ID: 13186248.

20 siRNA candidates were selected:

#	Position	Sequence
FGFR1-1	2701-2721	AACGGCCGACTGCCTGTGAAG
FGFR1-2	2275-2295	AAGTCGGACGCAACAGAGAAA
FGFR1-3	2422-2442	AAGGGCAACCTGCGGGAGTAC
FGFR1-4	2255-2275	AAGTGGCTGTGAAGATGTTGA
FGFR1-5	2319-2339	AATGGAGATGATGAAGATGAT
FGFR1-6	2237-2257	AACCCAACCGTGTGACCAAAG
FGFR1-7	2887-2907	AAGCCCAGTAACTGCACCAAC
FGFR1-8	1540-1560	AACGTGGAGTTCATGTGTAAG
FGFR1-9	2236-2256	AAACCCAACCGTGTGACCAAA
FGFR1-10	2332-2352	AAGATGATCGGGAAGCATAAG
FGFR1-11	1153-1173	AACACCAAACCAAACCGTATG
FGFR1-12	1303-1323	AATGGCAAAGAATTCAAACCT
FGFR1-13	2905-2925	AACGAGCTGTACATGATGATG
FGFR1-14	1636-1656	AACCTGCCTTATGTCCAGATC
FGFR1-15	2857-2877	AAGCTGCTGAAGGAGGGTCAC
FGFR1-16	1596-1616	AAAGCACATCGAGGTGAATGG
FGFR1-17	2230-2250	AAGGACAAACCCAACCGTGTG
FGFR1-18	2968-2988	AAGCAGCTGGTGGAAGACCTG
FGFR1-19	2254-2274	AAAGTGGCTGTGAAGATGTTG
FGFR1-20	1444-1464	AACCACACATACCAGCTGGAT

FIG. 17 (Cont'd.)

SS3.5.

FGFR3 gene: Human FGFR3, Accession: M58051, Gene ID: 182568
transcript variant 1, Accession: NM_000142, Gene ID: 13112046;
transcript variant 2, Accession: NM_022965, Gene ID: 13112047;
20 siRNA candidates were selected:

#	Position	Sequence
FGFR3-1	1969-1989	AACCTCGACTACTACAAGAAG
FGFR3-2	1627-1647	AAGATGATCGGGAAACACAAA
FGFR3-3	1588-1608	AAGGACCTGTCGGACCTGGTG
FGFR3-4	865-885	AAGGTGTACAGTGACGCACAG
FGFR3-5	2263-2283	AAGCAGCTGGTGGAGGACCTG
FGFR3-6	652-672	AAGCTGCGGCATCAGCAGTGG
FGFR3-7	1540-1560	AAGCCTGTCACCGTAGCCGTG
FGFR3-8	1571-1591	AAGACGATGCCACTGACAAGG
FGFR3-9	1321-1341	AACGCGTCCATGAGCTCCAAC
FGFR3-10	1297-1317	AAGCGACAGGTGTCCCTGGAG
FGFR3-11	2191-2211	AACTGCACACACGACCTGTAC
FGFR3-12	994-1014	AAGGAGCTAGAGGTTCTCTCC
FGFR3-13	1570-1590	AAAGACGATGCCACTGACAAG
FGFR3-14	982-1002	AACACCACCGACAAGGAGCTA
FGFR3-15	1873-1893	AAGTGCATCCACAGGGACCTG
FGFR3-16	331-351	AATGCCTCCCACGAGGACTCC
FGFR3-17	1813-1833	AAGGACCTGGTGTCCTGTGCC
FGFR3-18	2152-2172	AAGCTGCTGAAGGAGGGCCAC
FGFR3-19	1723-1743	AACCTGCGGGAGTTTCTGCGG
FGFR3-20	265-285	AAGGATGGCACAGGGCTGGTG

FIG. 17 (Cont'd.)

SS3.6.

FGFR4 gene: Human FGFR4, Accession: L03840, Gene ID: 182570
transcript variant 1, Accession: NM_002011, Gene ID: 47524172;
transcript variant 2, Accession: NM_022963, Gene ID: 47524176;
transcript variant 3, Accession: NM_213647, Gene ID: 47524174;
20 siRNA candidates were selected:

#	Position	Sequence
FGFR4-1	726-746	AAGGATGGACAGGCCTTTCAT
FGFR4-2	2403-2423	AAGGTCCTGCTGGCCGTCTCT
FGFR4-3	1743-1763	AAGCTGATCGGCCGACACAAG
FGFR4-4	1085-1105	AAAGACTGCAGACATCAATAG
FGFR4-5	292-312	AAGAGCAGGAGCTGACAGTAG
FGFR4-6	1657-1677	AAGCCAGCACTGTGGCCGTCA
FGFR4-7	753-773	AACCGCATTGGAGGCATTCGG
FGFR4-8	1833-1853	AAGGGAAACCTGCGGGAGTTC
FGFR4-9	1392-1412	AAGCTCTCCCGCTTCCCTCTG
FGFR4-10	1078-1098	AAGTCCTAAAGACTGCAGACA
FGFR4-11	1692-1712	AACGCCTCTGACAAGGACCTG
FGFR4-12	604-624	AAGCACCCTACTGGACACACC
FGFR4-13	1086-1106	AAGACTGCAGACATCAATAGC
FGFR4-14	1686-1706	AAAGACAACGCCTCTGACAAG
FGFR4-15	666-686	AACACCGTCAAGTTCCGCTGT
FGFR4-16	1454-1474	AAGCTCATCCCTGGTACGAGG
FGFR4-17	984-1004	AAGGTGTACAGCGATGCCCAG
FGFR4-18	1687-1707	AAGACAACGCCTCTGACAAGG
FGFR4-19	1764-1784	AACATCATCAACCTGCTTGGT
FGFR4-20	504-524	AATCTCACCTTGATTACAGGT

FIG. 17 (Cont'd.)

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SS4. HGF pathway

SS4.1.
HGF Receptor gene: Human HGF receptor (MET), Accession: NM_000245, Gene ID: 42741654:

#	Position	Sequence
MET-1	341-361	AACACCCATCCAGAATGTCAT
MET-2	505-525	AAGCCAATTTATCAGGAGGTG
MET-3	1494-1514	AAGTCCTCTTAACATCTATAT
MET-4	1021-1041	AATCAGGTTCTGTTCCATAAA
MET-5	2723-2743	AAGCCAGTGATGATCTCAATG
MET-6	3929-3949	AAGTGGATGGCTTTGGAAAGT
MET-7	3747-3767	AAGTAGCCAAAGGCATGAAAT
MET-8	1066-1086	AATGCCTCTGGAGTGTATTCT
MET-9	281-301	AAGTCCGAGATGAATGTGAAT
MET-10	2111-2131	AATGGCCACGGGACAACACAA
MET-11	1682-1702	AATGGCTACACACTGGTTATC
MET-12	2722-2742	AAAGCCAGTGATGATCTCAAT
MET-13	838-858	AAGGCTAAAGGAAACGAAAGA
MET-14	3154-3174	AAGCCCAACTACAGAAATGGT
MET-15	1681-1701	AAATGGCTACACACTGGTTAT
MET-16	1382-1402	AATAGGACACTTCTGAGAAAT
MET-17	734-754	AAAGTCCTTTCATCTGTAAAG
MET-18	1364-1384	AATCATGAGCACTGCTTTAAT
MET-19	2529-2549	AAGCAGGAAGGAACTTTACAG
MET-20	334-354	AACACCCATCCAGAATGTCAT

FIG. 17 (Cont'd.)

SS5. Other Pathways-1

SS5.1.

PAK4-1	AACTTCGAGCACCGCGTGCAC
PAK4-2	AAGACCATCGTGCGGGGCAGC
Hepsin-A	AAGGTGGCAGCTCTCACTGCG
Hepsin-B	AACAGCGAGGAGAACAGCAAC
Antrogen R-A	AAGACCTACCGAGGAGCTTTC
Antrogen R-B	AAGAGACTAGCCCCAGGCAGC

FIG. 17 (Cont'd.)

SS5.3.

HP BRCA2-A			AAGTCAACCACAGAGTCGTAT	247-268
HP BRCA2-B			AAGTAACGAGTGAGCCACGCT	215-235
NOXA-A			AAGTCGAGTGTGCTACTCAAC	238-258
NOX			AACTGAACTTCCGGCAGAAAC	277-297
Novel ZF Protein			AATGCGGAGAACACTAATTAT	345-365
Novel ZF Protein			AACTTCCATAAATGTGAAATC	381-401
NFAT4			AAGTGATACTCCCGCCTCAGC	726-746
NFAT4			AAGTAGCTGGCACTACGGGCA	752-772
Co-factor of SP1			AATCAGGTTCCAATGTGATGA	200-221
Co-factor of SP1			AAGGCTTAGCTCCCAAGCCTC	145-165
Ets2 Repressor			AAGGCAGATCCAGCTGTGGCA	194-214
Ets2 Repressor			AAGCCAGAGTCGTCCCCTGGC	171-191
PKC related			AAGTCTTCCGTTTTCTGAGAA	69-89
PKC related			AATGGTGCAGCAGAAATTGGA	126-136
PKC eta			AAGAAGGGCCACCAGCTGCTG	269-289
PKC eta			AACGTCACCGACGGCGGCCAC	389-409
Mitochondrial F0			AACCTCGGGCAGAAGAGGAGA	164-184
Mitochondrial F0			AACTGAAACGGATTGCCAGAG	211-231
Bcl-2 TF			AAGAAGCGATACAGGTCTCGT	91-111
Bcl-2 TF			AAGGTCTCGTAGTAGAGATCG	126-146
Bcl-2 A1			AACCTGGATCAGGTCCAAGCA	257-277
Bcl-2 A1			AATCTGAAGTCATGCTTGGAC	334-354
RAP1			AACAGAGGAGGACTACATTCC	267-287
RAP1			AACCACGAAATCACCAGCATC	379-399

FIG. 17 (Cont'd.)

SS5.4.

Hpv-16E6	AAGTTACCAGATTTATGCACA
Hpv-16E6	AACAGTTACTGCGACGTGAGG
Hpv-16E7	AATATATGTTAGATTTGCAAC
Hpv-16E7	AATAGATGGTCCAGCTGGACA
Hpv-18E6	AACACGGCGACCCTACAAGCT
Hpv-18E6	AACTTACAGAGGTATTTGAAT
Hpv-18E7	AAGGCAACATTGCAAGACATT
Hpv-18E7	AATAGATGGAGTTAATCATCA

SS5.5.

DICER -A	AB028449	AATGGGTCCTTTCTTTGGACT
DICER -B		AACTGCTTGAAGCAGCTCTGG
MD2 PROTEIN-A	NM_015364	AAGCTCAGAAGCAGTATTGGG
MD2 PROTEIN-B		AATGCAATACCCAATTTCAAT
GAGE-2-A	U19143	AATGATTGGGCCTATGCGGCC
GAGE-2-B		AAGTGGAACCAGCAACACCTG
BREAST TA 84-A	NM_015966	AAGACTTTGGAGGACTTCCGG
BREAST TA 84-B		AAGTCGCGGGGAGATAAACTG
EGFR-RP-A	AK026010	AAGCTGGACATTCCCTCTGCG
EGFR-RP-B		AAGAGCCCAGCTTCCTGCAGC
ENDOPLASMIN 94-A	AK025862	AACTGTTGAGGAGCCCATGGA
ENDOPLASMIN 94-B		AATCTGATGATGAAGCTGCAG
FOLATE BP-A	AF000381	AACCGCGGTCCTATTCCATTA
FOLATE BP-B		AACACTCCAATTTTTCAAAGT
RALA BP-A	NM_006788	AACACCGCAGGGTGGAGCATG
RALA BP-B		AAGAGATCAGCCCTACTAAGT
GRB2 BP-A	BC000631	AAGGGGGGACATCCTCAAGGT
GRB2 BP-B		AATCCCCAGAGCCAAGGCAGA
CDR-62-A	L02867	AAGCGCCAGGCCCCGCGTGGG
CDR-62-B		AAGAGGAGTCCTGGTACGACC
A-RAF-A	U33821	AAGAGTTACCTTCCTAATGCA
A-RAF-B		AAGATTGGGTTGGTATATTCA
NOVEL-1-A	NM_017873	AATCCTTGTTCTCACTGAGCT
NOVEL-1-B		AAGATGGCTGAGCTGGGGCTG
MAC30-A	L19183	AACCGACAGACTATGGGGGCT
MAC30-B		AACCTGCTGAAGTGGTATGCT
GRANULIN -A	NM_002087	AACGCGGTGCCCAGATGGTCA
GRANULIN -B		AATGGCCCACAACACTGAGCA
HCA ANTI. 58-A	NM_016436	AAGTGGGAGCCCAGTTGGAAG

FIG. 17 (Cont'd.)

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HCA ANTI. 58-B		AAGACATTGACTACGAGGAAG
MI2-BETA-A	NM_001273	AATGAAGAGGACCCAGAAGAG
MI2-BETA-B		AAGCCTAAGAAACCTCGGGAC
EGF FACTOR 8-A	NM_005928	AACCCCTGCCACAACGGTGGT
EGF FACTOR 8-B		AACCACTGTGAGACGAAATGT
APRIL-A	AK090698	AACTGCCCCAGCGATCTCTGC
APRIL-B		AACCTAATTCTCCTGAGGCTG
PGF PRECURSOR-A	AK023843	AAGAGTGACACTGTGGCTTCC
PGF PRECURSOR-B		AATGGGCTGAGCTGCTGCTCC
MELA. ANTIGEN-A	AB014518	AATCAGCTCAACACTGTCCTC
MELA. ANTIGEN-B		AAGGAGACAGTACTGAGTGCC
RALA B. PROTEIN-A	NM_006788	AACACCGCAGGGTGGAGCATG
RALA B. PROTEIN-B		AAGAGATCAGCCCTACTAAGT

FIG. 17 (Cont'd.)

SS6. siRNA Target Sequence for RSV

SS6.1.
Gene targets common to subgroups A and B (strains B1 and 9230 of RSV)

Target gene*	Sequence (5' to 3')**	Position on A2 (M734568)	Position on B1 (NC-001781)	Position on 9230 (AY353550)
Leader/NS1 (-) strand	AATGGGGCAAATAAGAATTTG	42-62	42-62	42-62
Leader/NS1	AATGGGGCAAATAAGAATTTg	42-62	42-62	42-62
N	AAGATGGCTCTTAGCAAAGTc	1137-1157	1137-1157	1135-1155
P	AATTCCTAGAATCAATAAAGg	2401-2421	2403-2423	2401-2421
M	AAGCTTCACGAAGGCTCCACA	3279-3299	3281-3301	3279-3299
SH	NA			
G	NA			
F	AATGATATGCCTATAACAAAt	6444-6464	6449-6469	6447-6467
M2	AAGATAAGAGTGTACAATACT	7975-7995	7987-8007	7986-8006
M2/L	NA			
L	AACATCCTCCATCATGGTTAA	9090-9110	9101-9121	9100-9120
L	AAGTACTAATTTAGCTGGACA	12973-12993	12984-13004	12983-13003
L	AAGATTGCAATGATCATAGTT	14133-14153	14144-14164	14143-14163
L	AACATTCATTGGTCTTATTTA	14243-14263	14254-14274	14253-14273

FIG. 17 (Cont'd.)

SS6.2.

Gene targets specific for subgroup A (Strains A2 & F/P of Long strains of RSV)

Target gene	Sequence (5' to 3')*	Position in A2 genome (M734568)
Leader (-) strand	AAATGCGTACAACAAACTTGC	9-29
Leader	AACAAACTTGCATAAACCAAA	19-39
NS1	AAGAATTTGATAAGTACCACT	54-74
NS1	AACTAACGCTTTGGCTAAGGC	209-229
NS2	AATAAATCAATTCAGCCAACC	602-622
NS2	AACTATTACACAAAGTAGGAA	830-850
N	AACAAAGATCAACTTCTGTCA	1176-1196
N	AAGAAATGGGAGAGGTAGCTC	1558-1578
P	AATTCAACTATTATCAACCCA	2520-2530
P	AACAATGAAGAAGAATCCAGC	2676-2696
M	AAATAAAGATCTGAACACACT	3770-3790
M	AAATATCCACACCCAAGGGAC	3442-3462
M	AAATAAAGATCTGAACACACT	3770-3790
SH	AACATAGACAAGTCCACACAC	4266-4286
SH	AACAATAGAATTCTCAAGCAA	4320-4340
G	AAACAAGGACCAACGCACCGC	4696-4716
G	AACTTCACTTATAATTGCAGC	4840-4860
F	AAATAAGTGTAATGGAACAGA	5858-5878
F	AAACAATCGAGCCAGAAGAGA	5969-5989
M2	AAATAAGTGGAGCTGCAGAGT	7781-7801
M2	AACAATCAGCATGTGTTGCCA	7880-7900
M2/L	NA	
L	AAGTTACATATTCAATGGTCC	8593-8613
L	AACTAAATATAACACAGTCCT	8685-8905
Trail	NA	

FIG. 17 (Cont'd.)

SS6.3.

Gene targets specific for subgroup B (Strains B1 and 9320)

Target gene	Sequence (5' to 3')*	Position in B1 genome (NC-001781)	Position in 9320 genome (AY353550)
Leader (-) strand	AATGCGTACTACAAACTTGCA	10-30	10-30
Leader	AAATGCGTACTACAAACTTGC	9-29	9-29
NS1	AATTAATTCTTCTGACCAATG	196-216	196-216
NS1	AACAAGCAGTGAAGTGTGCCC	278-298	278-298
NS2	AATAATAACATCTCTCACCAA	700-720	700-720
NS2	AATGTATTGGCATTAAGCCTA	936-956	936-956
N	AAATAAGGATCAGCTGCTGTC	1175-1195	1173-1193
N	AACAAACTATGTGGTATGCTA	1272-1292	1270-1290
P	AATAAAGGGCAAGTTCGCATC	2416-2436	2414-2434
P	AACAAATGACAACATTACAGC	2725-2745	2723-2743
M	AATATGGGTGCCTATGTTCCA	3361-3381	3359-3379
M	AACATACTAGTGAAGCAGATC	3428-3448	3426-3446
SH	AAATACATCCATCACAATAGA	4308-4328	4306-4326
SH	AAACATTCTGTAACAATACTC	4445-4465	4443-4463
G	AATCTATAGCACAAATAGCAC	4796-4816	4794-4814
G	AATATTCATCATCTCTGCCAA	4866-4886	4864-4884
F	AAAGAAACCAAATGCAATGGA	5858-5878	5856-5876
F	AAACAAAGCTGTAGTCAGTCT	6187-6207	6185-6205
M2	AAATAAGTGGAGCTGCTGAAC	7793-7813	7792-7812
M2	AACAATCAGCATGTGTTGCTA	7892-7912	7892-7911
M2/L	NA		
L	AAATAACATCACAGATGCAGC	9591-9611	9590-9610
L	AATACCTACAACAGATGGCCC	9931-9951	9930-9950
Trail	NA		

FIG. 17 (Cont'd.)

AMENDED SHEET

SS7

SS7.1. siRNA targeted sequences for SARS coronavirus inhibition

Name	Coding Region	Position (nt)	Sequence (5'-3')
SC07	5'UTR	146-166	aacgagtaactcgtccctctt
SC08	ORF1a, nsp-1	594-614	aattgcataccgcaatgttct
SC06	ORF1a, nsp-3	2721-2741	aacctttggagaagatactgt
SC03	ORF1a, nsp-3	2772-2792	aatcacatttgagcttgatga
SC09	ORF1a, nsp-3	3236-3256	aacctacacctgaagaaccag
SC10	ORF1a, nsp-3	4172-4192	aaggatgtgctggttatacac
SC11	ORF1a, nsp-3	5758-5778	aaaggaccagtgactgatgtt
SC12	ORF1a, nsp-3	8096-8116	aaggtgttgttgataccgatg
SC13	ORF1a, nsp-6	11074-11094	aagcacgcattcttgtgcttg
SC05	ORF1b, nsp-12	13530-13550	aaggatgaggaaggcaattta
SC01	ORF1b, nsp-12	13603-13623	aagagactatttataacttgg
SC16	ORF1b, nsp-12	14758-14778	aactcctattcgtagttgaag
SC17	ORF1b, nsp-13	16756-16776	aaggtgactatggtgatgctg
SC14	ORF1b, nsp-13	17544-17564	aaggataagtcagctcaatgc
SC18	ORF1b, nsp-14	18264-18284	aacctacctctccagctagga
SC15	ORF1b, nsp-16	20843-20863	aactggcacactacttgtcga
SC02	ORF2, Spike	21553-21573	aagctcctaattacactcaac
SC04	ORF2, Spike	21669-21689	aatgttacagggtttcatact
SC19	ORF2, Spike	22068-22088	aagggctatcaacctatagat
SC20	ORF2, Spike	22289-22309	aatcacagatgctgttgattg
SC21	ORF2, Spike	22951-22971	aaccttacagagttgtagtac
SC22	ORF2, Spike	23272-23292	aagatgttaactgcactgatg
SC23	ORF2, Spike	24871-24891	aagagctggacaagtacttca
SC37	ORF3a	25330-25350	aagtactgttcatgctacagc
SC38	ORF3a	25599-25619	aatgcatcaacgcatgtagaa
SC39	ORF3a	25618-25638	aattattatgagatgttggct
SC40	ORF3a	25764-25784	aaggtgacggcatttcaacac
SC41	ORF3a	25805-25825	aaattactacagacactggta
SC42	ORF3a	25929-25949	aaaatgctacattcttcatct
SC43	ORF3a	25984-26004	aatacacacaatcgacggctc
SC24	ORF4, E-protein	26121-26141	aagaaacaggtacgttaatag
SC25	ORF4, E-protein	26137-26157	aatagttaatagcgtacttct
SC34	ORF4, E-protein	26170-26190	aagcacattgacgcatacaaa
SC26	ORF4, E-protein	26219-26139	tgtgcgtactgctgcaatatt
SC36	ORF4, E-protein	26230-26250	aagactgatgaagctcagcct
SC27	ORF4, E-protein	26307-26327	aaggagttcctgatcttctgg
SC28	ORF5, M-protein	26440-26460	aacctagtaataggtttccta
SC29	ORF5, M-protein	26628-26648	aatggcttgtattgtaggctt
SC30	ORF5, M-protein	26760-26780	aattgtgaccagaccgctcat
SC33	ORF5, M-protein	26789-26809	aaccagcttgagagcaaagtt
SC31	ORF5, M-protein	26876-26896	aagagatcactgtggctacat
SC32	ORF5, M-protein	26968-26988	aaccgctaccgtattggaaac
SC44	ORF7	27355-27375	aaccttgcccatcaggaacat
SC45	ORF7	27425-27445	aacttgcactagcacacactt
SC46	ORF7	27541-27561	aagagctctactcgccacttt
SC47	ORF9a, N-protein	28176-28196	aactgacaataaccagaatgg
SC48	ORF9a, N-protein	28355-28375	aaattggctactaccgaagag

FIG. 17 (Cont'd.)

SC35	ORF9a, N-protein	28904-28924	aacagtacaacgtcactcaag

FIG. 17 (Cont'd.)

SS8, TNF pathway

TNF pathway

SS8.1.

TNF gene: human TNF (synonyms: DIF, TNFA, TNFSF2, TNF-alpha),

Accession : NM_000594, Gene ID: 25952110

10 siRNA candidates were selected:

#	Position	Sequence
hTNF-1	428-448	AAGCCTGTAGCCCATGTTGTA
hTNF-2	512-532	AATGGCGTGGAGCTGAGAGAT
hTNF-3	671-691	AACCTCCTCTCTGCCATCAAG
hTNF-4	533-553	AACCAGCTGGTGGTGCCATCA
hTNF-5	731-751	AAGCCCTGGTATGAGCCCATC
hTNF-6	497-517	AATGCCCTCCTGGCCAATGGC
hTNF-7	779-899	AAGGGTGACCGACTCAGCGCT
hTNF-8	181-201	AAGCATGATCCGGGACGTGGA
hTNF-9	665-685	AAGGTCAACCTCCTCTCTGCC
hTNF-10	180-200	AAAGCATGATCCGGGACGTGG

SS8.2.

hTNFR1 gene: human TNF receptor, 1A (synonyms: TNFRSF1A, FPF, p55, p60, TBP1, TNF-R, TNFAR, TNFR1,p55-R, CD120a, TNFR55, TNFR60, TNF-R-I, TNF-R55, MGC19588), Accession : NM_001065, Gene ID: 23312372

20 siRNA candidates were selected:

#	Position	Sequence
hTNFR1-1	666-686	AAGAACCAGTACCGGCATTAT
hTNFR1-2	1005-1025	AAGCTCTACTCCATTGTTTGT
hTNFR1-3	1320-1340	AAGCCACAGAGCCTAGACACT
hTNFR1-4	841-861	AAAGCCTGGAGTGCACGAAGT
hTNFR1-5	472-492	AAGGAACCTACTTGTACAATG
hTNFR1-6	714-734	AATTGCAGCCTCTGCCTCAAT
hTNFR1-7	605-625	AATGGGTCAGGTGGAGATCTC
hTNFR1-8	669-689	AACCAGTACCGGCATTATTGG
hTNFR1-9	471-491	AAAGGAACCTACTTGTACAAT
hTNFR1-10	462-482	AAGTGCCACAAAGGAACCTAC
hTNFR1-11	604-624	AAATGGGTCAGGTGGAGATCT
hTNFR1-12	810-830	AACGAGTGTGTCTCCTGTAGT
hTNFR1-13	888-908	AAGGGCACTGAGGACTCAGGC
hTNFR1-14	809-829	AAACGAGTGTGTCTCCTGTAG
hTNFR1-15	991-1011	AACGGTGGAAGTCCAAGCTCT
hTNFR1-16	768-788	AACACCGTGTGCACCTGCCAT
hTNFR1-17	732-752	AATGGGACCGTGCACCTCTCC
hTNFR1-18	1089-1109	AACCCAAGCTTCAGTCCCACT
hTNFR1-19	476-496	AACCTACTTGTACAATGACTG
hTNFR1-20	444-464	AATTCGATTTGCTGTACCAAG

FIG. 17 (Cont'd.)

SS8.3.

hTNFR2 gene: human TNF receptor, 1B (synonyms: TNFRSF1B, p75, TBPII, TNFBR, TNFR2, CD120b, TNFR80, TNF-R75, p75TNFR, TNF-R-II), Accession : NM_001066, Gene ID: 23312365. 20 siRNA candidates were selected:

#	Position	Sequence
hTNFR2-1	844-864	AAGGGAGCACTGGCGACTTCG
hTNFR2-2	957-977	AAGCCCTTGTGCCTGCAGAGA
hTNFR2-3	412-432	AAGCCTGCACTCGGGAACAGA
hTNFR2-4	1362-1382	AAGGAGGAATGTGCCTTTCGG
hTNFR2-5	294-314	AAGACCTCGGACACCGTGTGT
hTNFR2-6	351-371	AACTGGGTTCCCGAGTGCTTG
hTNFR2-7	784-804	AACCCAGCACTGCTCCAAGCA
hTNFR2-8	1301-1321	AATGGGAGACACAGATTCCAG
hTNFR2-9	979-1099	AAGCCAAGGTGCCTCACTTGC
hTNFR2-10	914-934	AATAGGAGTGGTGAACTGTGT
hTNFR2-11	1227-1247	AATGTCACCTGCATCGTGAAC
hTNFR2-12	600-620	AACACGACTTCATCCACGGAT
hTNFR2-13	1288-1308	AAGCCAGCTCCACAATGGGAG
hTNFR2-14	432-452	AACCGCATCTGCACCTGCAGG
hTNFR2-15	984-1004	AAGGTGCCTCACTTGCCTGCC
hTNFR2-16	800-820	AAGCACCTCCTTCCTGCTCCC
hTNFR2-17	954-974	AAGAAGCCCTTGTGCCTGCAG
hTNFR2-18	1245-1265	AACGTCTGTAGCAGCTCTGAC
hTNFR2-19	1369-1389	AATGTGCCTTTCGGTCACAGC
hTNFR2-20	776-796	AACTCCAGAACCCAGCACTGC

SS8.4.

mouse IL-1b	AGGCTCCGAGATGAACAACAA
mouse IL-1b	TACCTGTCCTGTGTAATGAAA
mouse IL-1r	ACCATCGAGGTTACTAATGAA
mouse IL-1r	TCGGAATATCTCCCATCATAA
mouse IL-1a	TCGGGAGGAGACGACTCTAAA
mouse IL-1a	CCAGAGTGATTTGAGATACAA
mouse IL-1r2	CACGTTTATCTCGGCTGCTTA
mouse IL-1r2	AAGACTGATAGTCCCGTGCAA
mouse TNF receptor a	AAGGAAAGTATGTCCATTCTA
mouse TNF receptor a	CCGCAACGTCCTGACAATGCA
mouse TNF receptor b	CCAGGTTGTCTTGACACCCTA
mouse TNF receptor b	CTGGCTATTCCCGGAAATGCA

FIG. 17 (Cont'd.)

mouse TNF	CACGTCGTAGCAAACCACCAA
mouse TNF	CAGCCGATTTGCTATCTCATA

FIG. 17 (Cont'd.)